PATENT SPECIFICATION

P-113-1
807,826

Date of Application and filing Complete Specification: March 14, 1956.

No. 8017/56.

Application made in Germany on March 14, 1955.

Complete Specification Published: Jan. 21, 1959.

Index at acceptance:—Class 2(3), B4(A1:A2:A4:D), C1(B2:B6:B10:D), C1E4K(4:8), C1F2(A3:A4:C3:C4:C5:D3), C1F4(A3:A4:D3:F2:F4:F5), C1G(5B:6A1:6A3:6B3), C2A(3:8:9:10:14), C2B3(A4:B:D:E:F:G4:G8), C2(B10:D19), C2R(15:16:17:18:20), C2T(17:21), C3A13C(2C:3C:6A:7:10D), C3C5(A4:C2:E1:E2), C5(A4:E1:E2).

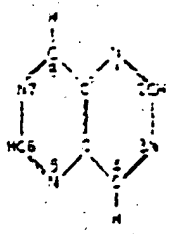
International Classification:—C07d.

COMPLETE SPECIFICATION

Derivatives of Pyrimido[5,4-d] Pyrimidine and production thereof

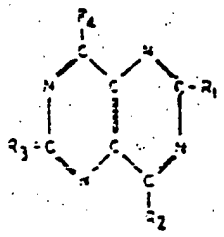
We, Dr. KARL THOMAE G.M.B.H., a Body Corporate organised under the laws of Germany, of Biberach an der Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a process for the production of derivatives of pyrimido [5,4-d] pyrimidine and with new compounds thereby obtained. Pyrimido [5,4-d] pyrimidine itself (also referred to as "homopurine") may be represented by the structural formula:—



I

According to the present invention pyrimido [5,4-d] pyrimidine derivatives are prepared by reacting pyrimido [5,4-d] pyrimidine-derivatives of the general formula:—



II

with compounds of the general formula:—

H—R or Me'—R III

In the above formula II at least one of the symbols R_1—R_4 represents a halogen-atom, whilst the other residues can have the following meaning: hydrogen substituted hydroxyl-groups, e.g. alkoxy-, aryloxy-, free or substituted thio- groups, e.g. alkylmercapto- and aryl- mercapto-groups, free or substituted amino-groups, e.g. mono- or di-alkylamino- or -arylamino-groups, the residue of a heterocyclic ring, e.g. the morpholine- or piperidine-ring. The substituents R_1—R_4 can among each other be the same or different. The symbol R in formula III signifies bromine, iodine, a substituted hydroxyl-group, e.g. an alkoxy- or aryloxy-group, free or substituted thio-group, e.g. carboxy alkylmercapto-, alkylmercapto- or arylmercapto-group, free or substituted amino-group, e.g. mono- or di-alkylamino- or -arylamino-group, free or substituted guanidino-group, free or substituted hydrazino-group, e.g. alkyl-, aryl- or acyl- hydrazino-group, or the residue of a heterocyclic ring, e.g. the morpholine- or piperidine-ring. Me' represents an alkali-metal.

The pyrimidopyrimidines of formula II used as starting materials may be obtained by any convenient method, for example by halogenation of the corresponding hydroxypyrimidopyrimidine or by ring closure of suitable reaction components.

The introduction of halogen into hydroxypyrimidopyrimidines, which may be produced for example by the methods described in British patent application No. 1383/55 (Serial No. 799,177), may be effected advantageously by heating with inorganic acid-halides, preferably phosphorus-halides, such as phosphorus oxychloride and phosphorus pentachloride. As examples of halogen-pyrimidopyrimidines obtained in this manner, may be mentioned: 2,4,6,8-tetrachloropyrimido-pyrimidine, 4,6,8-trichloro-pyrimido-pyrimidine, 4,6,8-trichloro-2-thio-pyrimido-pyrimidine, 6-methylthio-2,4-dichloro-pyrimido-pyrimidine.

[Price 3s. 6d.]

The halogenation of pyrimidopyrimidine-derivatives containing hydrogen and capable of further substitution can be achieved by the action of free halogens or halogen-releasing compounds, e.g. of N-halogensuccinimides, in inert solvents. It is also possible to obtain halogen-substituted pyrimidopyrimidine derivatives by ring-closure, for example by the reaction of nuclear-halogenated pyrimidine-4-carboxylic acids, substituted in the 5-position, with reaction components leading to the formation of the pyrimidopyrimidine-ring system as described in Patent Application 1383/55 (Serial No. 799,177).

As starting substances of the general formula II may be mentioned by way of examples 2,6 - dichloro - 4,8 - diamino-pyrimidopyrimidine, 2,6-dichloro-4,8-dianilino-pyrimidopyrimidine, 6-chloro-4,8-disemicarbazido-pyrimidopyrimidine, 6-chloro-2-thio-4,8-dimorpholine-pyrimidopyrimidine, 2,6-dichloro-4,8-diphenoxy-pyrimidopyrimidine, 2,6-dichloro-4,8-diphenylthio-pyrimidopyrimidine, 6-methylthio-2,4-dichloro-pyrimidopyrimidine, 4,6,8-trichloro-2-thio-pyrimidopyrimidine, 6-chloro-4,8-diiodo-pyrimidopyrimidine, 4,6,8-trichloro-pyrimidopyrimidine, 2,4,6,8-tetrachloro-pyrimidopyrimidine.

As examples of compounds of the general formula III, which are suitable for the reaction with the halogen- derivatives of the pyrimidopyrimidine, may be mentioned, among others, the following: alcohols, or alkali metal alcoholates, phenols or alkali metal phenolates, ammonia, primary or secondary amines, guanidines, hydrazines, amino-alcohols, alkali metal hydrosulphides, mercaptans, thiophenols, or thiophenolates, morpholine, piperidine.

Halogenation exchange is also easily possible, in that one can convert e.g. a chloro-pyrimido-pyrimidine into the corresponding iodine-compound with sodium iodide in acetone as solvent.

In many cases it is useful to have present an acid-binding agent, such as alkali metal hydroxide, alkali metal carbonate or tertiary amines, or if desired an excess of the reaction component of formula III, where this can also act as an acid-binding agent.

The reaction can take place in the absence or presence of solvents or diluents inert in the reaction, e.g. acetone, dioxan, benzene, xylene or dimethylformamide, and if desired with the use of pressure. Water and alcohols can likewise be used as solvents or diluents, especially in the absence of alkalis and at low temperatures, since under these conditions they practically do not react with the halogen-containing pyrimidopyrimidines. Also the second reaction-component of the formula III can, if it is liquid under the reaction-conditions, be used in excess as solvent or diluent.

The reaction is conveniently effected at temperatures between —20° and 250° C. If desired reaction accelerators can be added during the reaction, examples of which are copper and copper-salts.

If at least two of the substituents R_1—R_4 in the above-given formula II are halogen, the reaction can also be carried out step-wise. Whereas for example at low temperatures (room-temperature or cooling) mainly the halogen in position 4 and 8 is exchanged, at higher temperatures (e.g. 150—200° C.) all the halogen atoms present, including those in position 2 and 6, are replaced by other atoms or groups. Thus it is possible to obtain mixed substituted compounds of pyrimido [5,4-d] pyrimidine.

In certain halogen-containing derivatives the reaction with the compounds of formula III can also be so conducted, that not only halogen but in addition also other substituents, e.g. hydroxyl-, substituted hydroxyl-, amino- or substituted amino- groups, are exchanged with the residue R of the reaction component of formula III. Thus it is possible for example to convert 2,6 - dichloro - 4,8 - dihydroxypyrimidopyrimidine, 2,6-dichloro-4,8-diaminopyrimidopyrimidine and 2,6-dichloro-4,8-dipiperidino-pyrimidopyrimidine into 2,4,6,8-tetra-anilino-pyrimidopyrimidine by reaction with aniline.

For the better understanding of the invention the following examples are given only as illustration. The temperatures given in the examples are in degrees Centigrade.

EXAMPLE 1.

4,6,8-trimethoxy-pyrimidopyrimidine

From 4,6,8 - trichloro - pyrimidopyrimidine and sodium methylate.

4.7 g (0.02 mol) of 4,6,8-trichloro-pyrimidopyrimidine (Mp. = 172°, obtained by boiling 4,6,8 - trihydroxy - pyrimidopyrimidine with phosphorus pentachloride and phosphorus oxychloride under reflux) were introduced with cooling into 50 ccs of methanol-sodium methylate solution (0.12 mol of Na-methylate). After 6-hour standing at room temperature the mixture was neutralized with glacial acetic acid, the precipitate removed by filtration under suction and thoroughly washed with water and acetone. Yield 3.5 g (80% of theory). The colourless thin needles obtained after recrystallization from much methanol melt at 225—226° (sublimation as from 200° C.).

$C_9H_{10}O_3N_4$	calc.:	C 48.64	H 4.54	N 25.22
Mol. weight = 222.2	found:	48.48	4.55	25.18

EXAMPLE 2.

Various 2,6-dichloro-4,8-diamino-pyrimidopyrimidines

From tetrachloro-pyrimidopyrimidine and the corresponding amines at room-temperature.

a) 2,6-dichloro-4,8-di-(N-hydroxyethylanilino)-pyrimidopyrimidine.

Into a solution of 5.4 g (0.02 mol) of 2,4,6,8-tetrachloro-pyrimidopyrimidine in 50 ccs of dry dioxan were poured while stirring 10.9 g (0.08 mol) of N-hydroxyethylaniline (dissolved in 15 ccs of dioxan). With slight heat-development a yellowish, crystalline deposit quickly separated, which clearly consists mainly of N-hydroxyethylaniline-hydrochloride. By the addition of 200 ccs of water to the suspension obtained 2,6-dichloro-4,8-di-(N-hydroxyethylanilino)-pyrimidopyrimidine was finally precipitated, with a simultaneous dissolving of the hydrochloride, as a yellow, first somewhat sticky, but quickly solidifying deposit. Yield 8.1 g (86% of theory). For analysis the compound was several times recrystallised from methanol: luminous yellow, microcrystalline powder (prisms), Mp. = 189—190°.

$C_{22}H_{18}O_2N_6Cl_2$	calc.:	C 56.05	H 4.27	N 17.83
Mol. weight = 471.3	found:	56.12	4.52	17.61

As examples the following 2,6-dichloro-4,8-diamino-pyrimidopyrimidines analogous to the compound a) were inter alia produced:

b) 2,6 - dichloro-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 276—277°.

c) 2,6-dichloro-4,8-di-(p-chloranilino)-pyrimidopyrimidine, Mp. = 307—309°.

d) 2,6-dichloro-4,8-di-(β-hydroxyethylamino)-pyrimidopyrimidine, Mp. = 246—248°.

e) 2,6-dichloro-4,8-bis(β-diethylamino-ethylamino)-pyrimidopyrimidine, Mp. = 128—130°.

f) 2,6-dichloro-4,8-bis(methyl-dodecylamino)-pyrimidopyrimidine, Mp. = 76—77°.

g) 2,6-dichloro-4,8-bis(isoamylamino)-pyrimidopyrimidine, Mp. = 94—95°.

h) 2,6-dichloro-4,8-bis-(benzylamino)-pyrimidopyrimidine, Mp. = 229—230°.

i) 2,6 - dichloro - 4,8 - bis(p-dimethylamino-anilino) - pyrimidopyrimidine, no melting point up to 350°.

k) 2,6-dichloro-4,8-bis(diallylamino)-pyrimidopyrimidine, Mp. = 100—101°.

l) 2,6 - dichloro - 4,8-di-(methyl-cyclohexylamino) - pyrimidopyrimidine, Mp. = 179—181°.

m) 2,6 - dichloro-4,8-di-(β-chlorethylamino)-pyrimidopyrimidine, no melting point up to 350°.

n) 2,6 - dichloro-4,8-bis(butyl-ethanolamino)-pyrimidopyrimidine, Mp. = 140—141°.

o) 2,6-dichloro-4,8-bis(benzyl-ethanolamino)-pyrimidopyrimidine, Mp. = 173—175°.

p) 2,6 - dichloro-4,8-bis(2,3-dihydroxypropyl-amine) - pyrimidopyrimidine, Mp. = 208—210°.

q) 2,6 - dichloro - 4,8-diamino-pyrimidopyrimidine, no melting point up to 350°.

r) 2,6 - dichloro - 4,8-di-(carbethoxymethyl-amino) - pyrimidopyrimidine, Mp. = 207—209° (decomp.)

$C_{14}H_{12}N_6Cl_2$	calc.:	C 56.41	H 3.16	N 21.93	Cl 18.50
Mol. weight: 383.2	found:	56.61	3.42	21.79	Cl 18.81

EXAMPLE 3.

2,6-dichloro-4,8-diiodo-pyrimidopyrimidine

From 2,4,6,8-tetrachloro-pyrimidopyrimidine and sodium iodide. 1.4 g (0.005 mol) of tetrachloro-pyrimidopyrimidine (Mp. = 255—258°, obtained by melting 3-methyl-2,6,8-trihydroxy - 4 - oxo-3,4-dihydropyrimidopyrimidine (sodium salt) with phosphorus pentachloride, the 3-methyl group being removed during this process), and 4.5 g of sodium iodide were heated to boiling for 10 minutes in 50 ccs of acetone. After the removal of the separated sodium chloride by filtration under suction (the quantity of which corresponded to the exchange of 2-chlorine atoms) the reaction-product was precipitated out in colourless, small crystals by the addition of water to the solution: 2.1 g (93% of theory).

EXAMPLE 4.

2,6-dichloro-4,8-dianilino-pyrimido-pyrimidine

From 2,6-dichloro-4,8-diiodo-pyrimidopyrimidine and aniline. 4.5 g (0.01 mol) of 2,6-dichloro-4,8-diiodo-pyrimidopyrimidine were dissolved in 100 ccs of dry dioxan and added dropwise during the course of half an hour while stirring and ice-cooling into a solution of 3.7 g (0.04 mol) of aniline in absolute benzene. A precipitation of yellow crystals follows very quickly. After further stirring during half an hour the crude product was removed by suction, digested with weak aqueous hydrochloric acid, again removed by suction, washed and dried: 2.3 g (61% of theory). For analysis the compound was recrystallized three times from dioxan: very weakly yellow coloured small needles of Mp. = 287—288°.

EXAMPLE 5.

2,4,6,8-tetraanilino-pyrimido-pyrimidine

From 2,4,6,8 - tetrachloro-pyrimidopyrimidine and aniline. 2.7 g (0.01 mol) of tetrachloro-pyrimidopyrimidine (Mp. = 255—258°, obtained from 2,6-dichloro-4,8-dihydroxy-pyrimidopyrimidine by boiling with phosphorus oxychloride under reflux) were boiled under reflux for 25 minutes with 45 g of aniline. Upon pouring the dark-brown solu-

tion obtained into 500 ccs of 1N hydrochloric acid the crude tetraanilino-pyrimidopyrimidine precipitated as a brownish, amorphous deposit.

$C_{30}H_{24}N_8$	calc.:	C 72.56	H 4.87	N 22.57
Mol. weight: 496.6	found:	71.70	4.80	23.27

This compound could also be obtained by boiling with aniline according to the same method of working from 2,6-dichloro-4,8-dianilino-pyrimidopyrimidine, 2,6-dichloro-4,8-diamino-pyrimidopyrimidine, 2,6-dichloro-4,8-dihydroxy-pyrimidopyrimidine and 2,6-dichloro-4,8-dipiperidino-pyrimidopyrimidine.

EXAMPLE 6.

6-chloro-4,8-dimorpholino-pyrimidopyrimidine

From 6 - chloro-4,8-diiodo-pyrimidopyrimidine and morpholine.

Into a solution of 4.2 g (0.01 mol) of 6-chloro-4,8-diiodo-pyrimidopyrimidine (obtained from 4,6,8-trichloro-pyrimidopyrimidine and sodium iodide) in 50 ccs of dioxan were poured while stirring and cooling a mixture of 2.0 g (0.023 mol) of morpholine and 2.0 g (0.02 mol) of triethylamine, dissolved in 20 ccs of dioxan. After standing for about half an hour the initially separated amine-hydroiodide was again brought into solution by the addition of 400 ccs of water and the crude 6 - chloro - 4,8-dimorpholino-pyrimidopyrimidine precipitated. Yield 2.7 g (80% of theory). It was recrystallized three times from dioxan for analysis: long, colourless needles of Mp. = 199—200°.

$C_{16}H_{21}O_2N_6Cl$	calc.:	C 49.93	H 5.08	N 24.96
Mol. weight: 336.8	found:	49.41	4.92	24.81

EXAMPLE 7.

Various 4,6,8-triamino-pyrimidopyrimidines

From the corresponding 6-chloro-4,8-diamino-pyrimidopyrimidines by the reaction with the corresponding amines at higher temperature, if desired under pressure.

a) 6 - morpholino-4,8-bis(diethylamino)-pyrimidopyrimidine

6 g (about 0.02 mol) of 6-chloro-4,8-bis (diethylamino) - pyrimidopyrimidine were warmed to 180° for 1.5 hours in a tube with 3.4 g (0.04 mol) of morpholine. The greasy reaction-product could only be obtained as a solid mass after twice reprecipitating from very dilute hydrochloric acid and after prolonged standing. After drying in vacuo at room-temperature: 2.8 g. For analysis the substance was again recrystallized twice from methanol-water (2:1): ivory-coloured, shiny scales (small, irregular leaflets), Mp. = 73—75°.

$C_{14}H_{21}ON_7$	calc.:	C 60.14	H 8.13	N 27.27
Mol. weight: 359.5	found:	59.89	8.26	27.28

For example among others the following 4,6,8-triamino-pyrimidopyrimidines were produced analogous to the substance a):

b) 6-methylamino-4,8-bis(ethylamino)-pyrimidopyrimidine, Mp. = 94—96°.

c) 6-morpholino-4,8-di-(ethyl-ethanolamino)-pyrimidopyrimidine, Mp. = 120—122°.

d) 6-anilino-4,8-diamino-pyrimidopyrimidine, Mp. = 170—173°.

e) 6-diethanolamino-4,8-bis(allylamino)-pyrimidopyrimidine, Mp. = 104—106°.

f) 6-dimethylamino-4,8-diamino-pyrimidopyrimidine, Mp. = 292—294°.

g) 6 - diethanolamino - 4,8-dipiperidino-pyrimidopyrimidine, Mp. = 100—105° (sintering as from 95°).

h) 6-(β-hydroxyethylamino)-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 106—108°.

i) 6 - methylethanolamino - 4,8 - bis(methylamino) - pyrimidopyrimidine, Mp. = 64—66°.

k) 6 - morpholino - 4,8-di-(γ-methoxypropylamino) - pyrimidopyrimidine, Mp. = 80—82°.

l) 6 - diisopropanolamino - 4,8-dimorpholino-pyrimidopyrimidine, Mp. = 106—108°.

m) 6 - diethanolamino-4,8-di-(p-nitroanilino)-pyrimidopyrimidine, Mp. = 310—311°.

n) 6-piperidino-4,8-di(β-hydroxyethylamino)-pyrimidopyrimidine, Mp. = 178—179°.

o) 6 - diethanolamino-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 150—152°.

p) 6 - morpholino - 4,8-bis(ethylamino)-pyrimidopyrimidine, Mp. = 151—153°.

q) 6-morpholino-4,8-diamino-pyrimidopyrimidine, Mp. = 266—267°.

EXAMPLE 8.

Various 2,4,6,8-tetraamino-pyrimidopyrimidines

From 2,4,6,8 - tetrachloro - pyrimidopyrimidine and the corresponding amines at elevated temperature, if desired under pressure and with the addition of copper-powder or copper-salts.

a) 2,4,6,8 - tetra - (dimethylamino)-pyrimidopyrimidine

2.7 g (0.01 mol) of tetrachloro-pyrimidopyrimidine were stirred in small portions into 50 ccs of an absolute alcohol-dimethylamine solution (0.14 mol), whereby the dichlorodiamino-compound separates and the thus obtained suspension was heated for an hour to 200° in a bomb-tube after the addition of 0.1 g of copper sulphate. The crude reaction-product which separated upon diluting the obtained solution with water was once repre-

cipitated dissolving in 200 ccs of 0.2N-hydrochloric acid, treatment with animal charcoal, precipitation with conc. ammonia). Yield 1.7 g (56% of theory). For analysis the substance was recrystallized three times from absolute alcohol and dried at 130° C. and 0.1 Torr. Luminous yellow, irregular needles, Mp. = 164—165°.

$C_{14}H_{24}N_8$ calc.: C 55.22 H 7.95 N 36.81
Mol. weight = 304.4 found: 55.33 7.86 36.78

Among others the following 2,4,6,8-tetraamino-pyrimidopyrimidines were produced analogous to compound a):

b) 2,4,6,8-tetrakis(allylamino)-pyrimidopyrimidine, Mp. = 201—202°.
c) 2,4,6,8-tetrakis(methyl-ethanolamino)-pyrimidopyrimidine, Mp. = 155—156°.
d) 2,4,6,8 - tetra-(β-hydroxyethylamino)-pyrimidopyrimidine, Mp. = 180—182°.
e) 2,4,6,8-tetrapiperidino-pyrimidopyrimidine, Mp. = 163—165°.
f) 2,4,6,8-tetramorpholino-pyrimidopyrimidine, Mp. = 266—268°.
g) 2,4,6,8-tetra-(p-chloranilino)-pyrimidopyrimidine, Mp. = over 330°.
h) 2,4,6,8-tetraamino-pyrimidopyrimidine, no melting-point up to over 350°.
i) 2,4,6,8-tetra-methylamino-pyrimidopyrimidine, Mp. = 202—204°.

Example 9.

Various 6-chloro-4,8-diamino-pyrimidopyrimidines

From 4,6,8 - trichloro-pyrimidopyrimidine and the corresponding amines at room-temperature, if desired with cooling.

a) 6-chloro-4,8-di-allylamino-pyrimidopyrimidine

To a solution of 4.8 g (about 0.02 mol) of 4,6,8-trichloro-pyrimidopyrimidine in 50 ccs of dry dioxan were added while stirring 4.6 g (0.08 mol) of allylamine in 15 ccs of dioxan; slight self-warming occurred. After standing for a short time the crude reaction-product was precipitated as a yellowish, amorphous deposit by the addition of water, removed by filtration under suction and dried in vacuo at room-temperature. Yield 4.8 g (87% of theory). For purification the crude 6-chloro-4,8-di-allylamino-pyrimidopyrimidine was twice recrystallized from ethanol. The thus obtained fine, colourless little needles melt at 114—116°.

Among others the following 6-chloro-4,8-diamino-pyrimidopyrimidines were produced analogous to compound a):

b) 6-chloro-4,8-di-(methyl-ethanolamino)-pyrimidopyrimidine, Mp. = 90—92°.
c) 6-chloro-4,8-bis(diisopropanolamino)-pyrimidopyrimidine, Mp. = 177—179°.
d) 6 - chloro-4,8-bis(methylamino)-pyrimidopyrimidine, Mp. = 227—229°.
e) 6-chloro-4,8-bis(diethanolamino)-pyrimidopyrimidine, Mp. = 135—136°.
f) 6 - chloro-4,8-di-(p-nitroanilino)-pyrimidopyrimidine, up to 350° no melting point.
g) 6-chloro-4,8-di-(3-methoxy-propylamino)-pyrimidopyrimidine, Mp. = 98—100°.
h) 6 - chloro-4,8-di-(o-methoxy-anilino)-pyrimidopyrimidine, Mp. = 290—292°.
i) 6 - chloro-4,8-bis(dibenzylamino)-pyrimidopyrimidine, Mp. = 160—163°.
k) 6 - chloro - 4,8-di-ethylenediamino-pyrimidopyrimidine, from 130° yellow colouration and decomposition at about 170°.
l) 6-chloro-4,8-disemicarbazido-pyrimidopyrimidine, no melting point up to 360°.

Example 10.

2,6-bis(β-diethylamino-ethoxy)-4,8-bis(diethylamino)-pyrimidopyrimidine

From 2,6 - dichloro-4,8-bis(diethylamino)-pyrimidopyrimidine, β - diethylaminoethanol and sodium.

3.4 g (0.01 mol) of 2,6-dichloro-4,8-bis(diethylamino) - pyrimidopyrimidine (obtained from tetrachloro-pyrimidopyrimidine and diethylamine) were boiled under reflux for 3 hours in a solution of 0.5 g of sodium in 35 g of β-diethylamino-ethanol (no visible change). The reaction-mixture was taken up in 300—400 ccs of water and the solution obtained after acidifying with conc. hydrochloric acid was treated with animal charcoal and filtered. On addition of conc. ammonia the pyrimidopyrimidine first separated as a heavy oil which after decanting, renewed addition of water and some standing with simultaneous cooling solidified. It was removed by filtration under suction and dried in vacuo at room-temperature: 3.2 g (64% of theory). For analysis the compound was purified by taking up in petroleum ether, treatment with animal charcoal and slowly evaporating off the solvent: colourless, soft mass of Mp = 35.5—37°.

$C_{24}H_{52}O_2N_8$ calc.: C 61.87 H 9.58 N 22.21
Mol. weight: 504.7 found: 61.83 9.53 22.56

Example 11.

6-chloro-2-thio-4,8-dimorpholino-pyrimidopyrimidine

From 4,6,8 - trichloro - 2 - thio - pyrimidopyrimidine and morpholine.

To a solution of 2.7 g (0.01 mol) of 4,6,8-trichloro-2-thio-pyrimidopyrimidine (obtained from 4,6,8-trihydroxy-2-thio-pyrimidopyrimidine (sodium salt) by boiling with phosphorus pentachloride in phosphorus oxychloride under reflux) in 50 ccs of dry dioxan were added while cooling 3.4 g (0.04 mol) of morpholine (dissolved in 10 ccs of dioxan). The crystal-suspension which immediately formed was, after standing for half an hour, mixed with a 5-fold volume of water and the crude reaction-product removed by filtration under suction, washed and dried: 1.6 g (43% of theory). For

analysis the 6-chloro-2-thio-4,8-dimorpholino-pyrimidopyrimidine was twice recrystallized from glacial acetic acid: strong yellow, amorphous powder of Mp = 240°.

$C_{14}H_{17}O_2N_6ClS$	calc.:	C 45.58 H 4.64
Mol. weight: 368.8	found:	45.46 4.42

EXAMPLE 12.

6-chloro-2-thio-4,8-dipiperidino-pyrimidopyrimidine

From 4,6,8-trichloro-2-thio-pyrimidopyrimidine and piperidine.

The production of this compound is carried through in the same manner as that of the morpholine-compound. Yield 1.1 g (30% of theory). After twice recrystallizing from butanol, orange-coloured, amorphous powder of Mp. = 242—243°.

$C_{14}H_{21}N_6ClS$	calc:	C 52.70 H 5.80
Mol. weight = 364.7	found:	52.13 5.72

EXAMPLE 13.

6-methylthio-2,4-dimorpholino-pyrimidopyrimidine

From 6-methylthio-2,4-dichloro-pyrimidopyrimidine and morpholine.

Into a solution of 1 g (0.004 mol) of 6-methylthio - 2,4 - dichloro - pyrimidopyrimidine (Mp. = 100—103°, obtained from 6-methylthio - 2,4 - dihydroxy - pyrimidopyrimidine (sodium salt) and phosphorus-pentachloride in phosphorus oxychloride under reflux) in 100 ccs of dioxan were poured while stirring 2.6 g (0.03 mol) of morpholine and the mixture was thereupon left to stand for about 14 hours. When the reaction-product did not separate even after the addition of 100 ccs of water, the solution was considerably evaporated in vacuo. The yellow flakes which separated were removed by suction, washed and dried: 0.6 g (46 % of theory). For analysis the 6-methylthio-2,4-dimorpholino-pyrimidopyrimidine was recrystallized four times from methanol: strong yellow, small, irregular crystals of Mp. = 130—132°.

$C_{17}H_{24}O_2N_6S$	calc:	C 48.26 H 5.78
Mol. weight: 348.4	found:	49.07 5.32

EXAMPLE 14.

2,6-diethoxy-4,8-bis(β-diethylamino-ethylamino)-pyrimidopyrimidine

From 2,6-dichloro-4,8-bis(β-diethylamino-ethylamino)-pyrimido-pyrimidine and sodium ethylate.

4.3 g (0.01 mol) of 2,6-dichloro-4,8-bis(β-diethylamino - ethylamino) - pyrimidopyrimidine were heated with 50 ccs of an absol. alcoholic-sodium alcoholate-solution (0.02 mol) in a bomb-tube for one hour to 190—200°. After cooling and removal by suction of the separated sodium chloride and rewashing with absol. alcohol the ethanol was evaporated off in vacuo. The residual, initially still oily pyrimidopyrimidine-derivative solidified upon treatment with 200 ccs of ice-water. After trituration in a mortar, it was removed by suction, washed and dried in vacuo at room-temperature. Yield 4.1 g (92 % of theory). For purification the compound was reprecipitated four times from hot, dilute hydrochloric acid and recrystallized once from petroleum ether: colourless little needles, Mp. = 78—78.5°.

Analysis: $C_{22}H_{40}O_2N_8$	calc:	C 58.92	H 8.92 N 24.99
Mol. weight: 448.6	found:	59.13	8.86 24.70

EXAMPLE 15.

2,4,6,8-tetraphenoxy-pyrimidopyrimidine

From 2,4,6,8-tetrachloro-pyrimidopyrimidine and phenol. Into a melt warmed to about 50° of 2.7 g (0.01 mol) of tetrachloro-pyrimidopyrimidine in 3.8 g (0.04 mol) of phenol were introduced 2.2 g (0.02 mol) of sodium carbonate and the mixture thereupon heated for 1 hour to 180°. After cooling it was taken up in 150 ccs of water and the tetraphenoxy - pyrimidopyrimidine, practically insoluble in aqueous medium, removed by suction after standing a short time. Yield: 4.6 g (92% of theory). For an analysis the compound was recrystallized once from benzene and twice from dimethylformamide: microcrystalline, partly rhomboidal, colourless leaflets, Mp. = 289—290°.

$C_{32}H_{20}O_4N_4$	calc.:	C 71.99 H 4.03 N 11.19
Mol. weight = 500.5	found:	70.86 4.20 11.56

EXAMPLE 16.

2,4,6,8-tetraphenylthio-pyrimido-pyrimidine

From 2,4,6,8-tetrachloro-pyrimidopyrimidine and thiophenol. Into a warm solution of 4.4 g (0.04 mol) of thiophenol and 1.6 g (0.04 mol) of sodium hydroxide in 50 ccs of moist dioxan were stirred 2.7 g (0.01 mol) of tetrachloro-pyrimidopyrimidine (dissolved in 50 ccs of dioxan). The 2,4,6,8-tetraphenylthio-pyrimidopyrimidine which separated immediately in almost pure form as short, yellow-green little needles, was removed by suction after the addition of 100 ccs of water, washed with water and dried at 110°. Yield 5.4 g (95% of theory). For analysis the compound was recrystallized twice from dimethylformamide: luminous yellow, microcrystalline prisms, Mp. = 240—244°.

$C_4H_2N_4S_4$ calc.: C 63.80 H 3.57 N 9.92
Mol. weight: 564.7 found: 63.11 3.31 9.55

EXAMPLE 17.

2,4,6,8-tetrathio-pyrimidopyrimidine

From 2,4,6,8-tetrachloro-pyrimidopyrimidine and sodium hydrosulphide.

5.4 g (0.02 mol) of tetrachloro-pyrimidopyrimidine and 5.6 g (0.1 mol) of sodium hydrosulphide were dissolved in 150 ccs of dimethylformamide and then boiled under reflux for 30 minutes. The reaction-solution was poured into 1.5 litres of water and after filtering the crude 2,4,6,8-tetrathio-pyrimidopyrimidine was precipitated out by acidification with hydrochloric acid as a dark-red amorphous deposit. After removal by suction, washing and drying 5.0 g of substance (96% of theory) were obtained. For purification the compound was recrystallized three times from dimethylformamide (animal-charcoal): carmine-red, microcrystalline powder (small needles or whetstones), no melting-point up to 350°.

EXAMPLE 18.

2,6-dichloro-4,8-diethylthio-pyrimidopyrimidine

From 2,4,6,8-tetrachloro-pyrimidopyrimidine and ethylmercaptan. Into a solution of 2.7 g (0.01 mol) of tetrachloro-pyrimidopyrimidine and 6 ccs (about 0.06 mol) of ethyl mercaptan (90%) in 50 ccs of dioxan were added dropwise while cooling and stirring 1.6 g (0.02 mol) of pyridine. An orange-coloured deposit separated. After standing for about one hour the reaction-mixture was taken up in 200 ccs of water, whereby the initially resulting deposit dissolved and the crude reaction-product separated as a red oil. After standing for about 14 hours the crude pyrimidopyrimidine-derivative which meantime had become solid was removed by suction, washed and dried: the colour had become lighter. Yield 3.1 g (96% of theory). For purification the crude compound was boiled once with methanol and recrystallized twice from ethanol: small colourless prisms, Mp. = 190—192°.

EXAMPLE 19.

Various 4,8-diamino-pyrimidopyrimidines

From 4,8-dichloro-pyrimidopyrimidine and the corresponding amino-compounds.

Into a solution of 4,8-dichloropyrimidopyrimidine (Mp. = 232°, produced from 4,8-dihydroxypyrimidopyrimidine (sodium salt) and phosphorus pentachloride in phosphorus oxychloride by boiling under reflux) in dioxan was poured in each case a fourfold molar quantity of the corresponding amino-compound (if necessary likewise dissolved). The reaction-product was then precipitated out by the addition of water and the yield determined. For purification (for analysis) the product was in each case reprecipitated from dilute hydrochloric acid and recrystallized from a suitable solvent.

a) 4,8-dimorpholino-pyrimidopyrimidine

From 4,8-dichloro-pyrimidopyrimidine and morpholine. Yield 98% of theory. From benzene very small colourless prisms, Mp. = 197—198°.

b) 4,8-dipiperidino-pyrimidopyrimidine

Yield 93% of theory. From methanol colourless, shiny scales, Mp. = 132—134°.

c) 4,8-dianilino-pyrimidopyrimidine

Yield 93% of theory. From dimethylformamide weakly yellow little needles. Mp. = 257—258°.

d) 4,8-diamino-pyrimidopyrimidine

Yield 99%. After reprecipitation from dilute hydrochloric acid: very small, colourless little needles, no melting up to 260°.

e) 4,8-bis(methylamino)-pyrimidopyrimidine

Yield 92%. From water colourless crystal-powder, Mp. = 265°.

f) 4,8-bis(dimethylamino)-pyrimidopyrimidine

Yield 97%. From water strong, shiny needles, Mp. = 115°.

g) 4,8-dihydrazino-pyrimidopyrimidine

Yield of analytically pure compound 93%. After reprecipitation from dilute hydrochloric acid: ivory-coloured, microcrystalline powder (very small needles), Mp. = 226°.

h) 4,8-bis(N,N'-diphenylguanidino)-pyrimidopyrimidine

Yield 80%. After reprecipitation from dilute hydrochloric acid: yellow, microcrystalline powder, Mp. = 245° (sinters at 200°).

i) 4,8-di-(β-hydroxyethylamino)-pyrimidopyrimidine

Yield of an analytically pure substance 72%, from methanol colourless rectangular leaflets and prisms, Mp. = 204—205°.

k) 4,8-di-(N-hydroxyethyl-p-nitroanilino)-pyrimidopyrimidine

Yield 73%. From dimethylformamide yellow, amorphous powder, Mp. = 265—267°.

EXAMPLE 20.

4,8-dithio-pyrimidopyrimidine

From 4,8-dichloro-pyrimidopyrimidine and potassium hydrosulphide. To a solution of 3.0 g (0.015 mol) of 4,8-dichloro-pyrimidopyrimidine in 100 ccs of dioxan were added 25 ccs of a concentrated alcoholic potassium hydrosulphide-solution. After standing for a short time at room-temperature the 4,8-dithio-pyrimidopyrimidine was precipitated out after the addition of water by acidification with dilute hydrochloric acid. Yield 2.8 g (96% of theory). The orange-coloured, amorphous powder obtained after twice reprecipitating from dilute ammonia shows no melting-point up to 350°.

EXAMPLE 21.

2,6-dimorpholino-4,8-diethylthio-pyrimidopyrimidine

From 2,6-dichloro-4,8-diethylthio-pyrimidopyrimidine and morpholine.

3.2 g (0.01 mol) of the 2,6-dichloro-4,8-

diethylthio - pyrimidopyrimidine obtained according to example 27 were heated to 200° for 2 hours in a bomb-tube with 20 ccs of morpholine, 20 ccs of water and 1 cc of cold-saturated copper sulphate-solution. The cooled reaction-mixture was taken up in about 200 ccs of water and after acidification with concentrated hydrochloric acid the 2,6-dimorpholino - 4,8 - diethylthio - pyrimidopyrimidine remaining undissolved was removed by suction, washed and dried at 110°. Yield 1.3 g (31% of theory). For analysis the substance was recrystallized twice from dimethylformamide: strong orange-coloured, microcrystalline prisms, Mp. = 293—295°.

$C_{18}H_{26}O_2N_6S_2$ calc: C 51.16 H 6.20
Mol. weight = 422.6 found: 51.06 6.31

EXAMPLE 22.

2,4,6,8-tetraethylthio-pyrimidopyrimidine

From tetrachloro-pyrimidopyrimidine and ethylmercaptan in the presence of pyridine.

2.7 g (0.01 mol) 2,4,6,8-tetrachloro-pyrimidopyrimidine were heated to 150° for 50 hours with 12 ccs (about 0.12 mol) of ethyl mercaptan (90%) and 3.2 g (0.04 mol) of pyridine in 50 ccs of dioxan. After decanting off from a viscous tarry mass the red-brown reaction-solution was mixed with 200 ccs of 0.5 N hydrochloric acid. The reaction product which separates first as an oil, but soon sets, was removed by suction and recrystallized once from ethanol. Yield 2.3 g (62% of theory). For analysis the compound was twice more recrystallized from ethanol: very small, brownish yellow prisms, Mp. = 140—141°.

$C_{14}H_{20}N_4S_4$ calc: C 45.13 H 5.41
Mol. weight: 372.6 found: 45.14 5.51

EXAMPLE 23.

6-morpholino-4,8-di-(carboxymethylthio)-pyrimidopyrimidine

From 6-chloro-4,8-di-(carboxymethylthio)-pyrimidopyrimidine and morpholine.

3.5 g (0.01 mol) of 6-chloro-4,8-di-(carboxymethylthio)-pyrimidopyrimidine of Mp. = 185—187° (produced from 4,6,8-trichloro-pyrimidopyrimidine and thioglycollic acid in the presence of pyridine with cooling) were heated to 100° for 45 minutes with 5ccs (0.06 mol) of morpholine. The reaction-mixture was taken up in 50 ccs of water and after separation of a tough deposit from the filtrate the 6-morpholino - 4,8 - di - carboxymethylthio-pyrimidopyrimidine was precipitated out by acidification with dilute hydrochloric acid as a light-yellow, flaky precipitate. For purification the compound was reprecipitated three times from dilute ammonia. One obtained a deep-yellow, amorphous powder of Mp. = 241—242° (from 220° dark colouration). Yield 0.9 g (23% of theory).

$C_{12}H_{16}O_5N_4S_2$ calc: C 35.81 H 2.51
Mol. weight: 402.4 found: 35.98 2.69

EXAMPLE 24.

4,6,8-tri-(carboxymethylthio)-pyrimido-pyrimidine

From 4,6,8-trichloro-pyrimidopyrimidine and thioglycollic acid in the presence of pyridine.

2.35 g (0.01 mol) of 4,6,8-trichloro-pyrimidopyrimidine were heated to 200° in a bomb-tube for 2 hours with 9.2 g (0.1 mol) of thioglycollic acid and 7.9 g (0.1 mol) of pyridine. Upon taking up the reaction-mixture in about 200 ccs of water and acidifying with hydrochloric acid the 4,6,8-tri-(carboxymethylthio)-pyrimidopyrimidine separated as light-yellow deposit. Yield 2.2 g (55% of theory). For analysis the substance was reprecipitated three times from dilute ammonia: small, light-yellow needles, Mp. = 230—231° (towards 190° dark colouration).

EXAMPLE 25.

6-carboxymethylthio-4,8-di-propyl-amino-pyrimidopyrimidine

From 6 - chloro - 4,8 - di - propylamino-pyrimidopyrimidine and thioglycollic acid in the presence of pyridine.

2.8 g (0.01 mol) of 6-chloro-4,8-di-propyl-amino - pyrimidopyrimidine (Mp. = 88—90° from 4,6,8-trichloro-pyrimidopyrimidine and propylamine) were heated to 200° in a bomb-tube for 2 hours with 9.2 g (0.1 mol) of thioglycollic acid and 7.9 g (0.1 mol) of pyridine. After washing the reaction-mixture with 150 ccs of water the 6-carboxymethylthio-4,8-di-propylamino-pyrimidopyrimidine was precipitated by acidification as a brown, initially greasy deposit. Yield 3.2 g (95 %). For analysis one reprecipitated twice from dilute caustic soda and recrystallized twice from a little methanol: brownish, small prisms, Mp. = 172—174°.

$C_{14}H_{20}O_2N_4S$ calc: C 49.98 H 5.99
Mol. weight: 336.4 found: 50.13 6.02

EXAMPLE 26.

Various 2,4,6,8-tetraamino-pyrimido-pyrimidines

From the corresponding 2,6-dichloro-4,8-diamino-pyrimidopyrimidines by reaction with the corresponding amines at elevated temperature.

a) 2,6 - bis(diethanolamino) - 4,8 - dipiperidino-pyrimidopyrimidine

36.7 g (0.1 mol) of 2,6-dichloro-4,8-dipiperidino-pyrimidopyrimidine (Mp. = 241—242°, produced from tetrachloro-pyrimido-pyrimidine and piperidine at room-temperature) were warmed to 200° with 100 g of diethanolamine and left for 10 minutes at this temperature. After cooling, the reaction-mixture was mixed with about 500 ccs of water, whereby the new substance separated as a viscous mass. After decanting the water it was digested with a little acetone and thus obtained as a solid yellow deposit. Yield 26.5 g (52.4%). For analysis the compound was recrystallized four times from ethyl acetate: deep-yellow, fine little needles, Mp. = 162—163°.

$C_{24}H_{40}O_4N_8$	calc.:	C 57.12 H 7.99 N 22.21
Mol. weight: 504.6	found:	57.16 7.83 22.26

Among others the following 2,4,6,8-tetraamino-pyrimidopyrimidines were produced analogous to the compound a):

b) 2,6 - bis(diethanolamino) - 4,8 - bis - (diethylamino)-pyrimidopyrimidine, Mp. = 167—168°.

c) 2,6-bis(diethanolamino)-4,8-dipyrrolidino-pyrimidopyrimidine, Mp. = 186—187°.

d) 2,6 - bis(diethanolamino) - 4,8 - bis(diallylamino)-pyrimidopyrimidine, Mp. = 110°.

e) 2,6 - bis(diethanolamino) - 4,8 - bis(dimethylamino)-pyrimidopyrimidine, Mp. = 182—183°.

f) 2,6 - bis(diethanolamino) - 4,8 - bis(dibutylamino) - pyrimidopyrimidine, Mp. = 124—126°.

g) 2,6 - di - (methyl - ethanolamino) - 4,8 - dipiperidino-pyrimidopyrimidine, Mp. = 122—124° (after sintering from 114°).

h) 2,6-di-(propylethanolamino)-4,8-dimorpholine-pyrimidopyrimidine, Mp. = 138—139°.

i) 2,6 - bis(diisopropanolamino) - 4,8 - dipiperidino-pyrimidopyrimidine, Mp. = 182—183°.

k) 2,6-di-(methyl-ethanolamino)-4,8-di-(dodecyl - ethanolamino) - pyrimidopyrimidine, Mp. = 88—90°.

$C_{32}H_{54}O_4N_8$	calc.:	C 55.44 H 7.61 N 23.52
Mol. weight: 476.6	found:	55.42 7.67 23.32

Among others the following 2,4,6,8-tetraamino-pyrimidopyrimidines were produced analogous to substance a):

b) 2,6 - dimorpholino - 4,8 - di - (propylethanolamino) - pyrimidopyrimidine, Mp. = 141—143°.

c) 2,6 - dimorpholino - 4,8 - di - (methylethanolamino) - pyrimidopyrimidine, Mp. = 207—209°.

d) 2,6-dimorpholino-4,8-bis(diethanolamino)-pyrimidopyrimidine, Mp. = 209—210°.

e) 2,6-dipiperidino-4,8-bis(diethanolamino)-pyrimidopyrimidine, Mp. = 182—184°.

f) 2,6 - bis(diethylamino) - 4,8 - bis(diethanolamino) - pyrimidopyrimidine, Mp. = 158—160°.

g) 2,6-dimorpholino-4,8-bis(dimethylamino)-pyrimidopyrimidine, Mp. = 192—193°.

h) 2,6 - dipiperidino - 4,8 - bis(isoamylamino)-pyrimidopyrimidine, Mp. = 192—194°.

l) 2,6-bis(diethanolamino)-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 202—204°.

EXAMPLE 27.

Various 2,4,6,8-tetraamino-pyrimido-pyrimidines

From the corresponding 2,6-dichloro-4,8-diamino-pyrimidopyrimidines by reaction with the corresponding amines at higher temperatures under pressure.

a) 2,6 - dimorpholino - 4,8 - di - (ethylethanolamino)-pyrimidopyrimidine

7.6 g (0.02 mol) of 2,6-dichloro-4,8-di-(ethylethanolamino)-pyrimidopyrimidine were heated to 200° for one hour in a bomb-tube with 20 ccs of morpholine. On taking up the reaction mixture in 200 ccs of water the crude tetramino-pyrimidopyrimidine separated as a yellow, amorphous deposit. It was removed by suction, washed and dried at 110°. Yield 8.7 g (91% of theory). For analysis the compound was recrystallized four times from methanol. The thus obtained light-yellow, microcrystalline little needles were dried at 130° and 0.1 Torr (Mp. = 190—191°).

i) 2,6-dipiperidino-4,8-dipyrrolidino-pyrimidopyrimidine, Mp. = 254—256°.

k) 2,6 - dipiperidino - 4,8 - di - (benzylethanolamino) - pyrimidopyrimidine, Mp. = 161—163°.

EXAMPLE 28.

Various 4,6,8-triamino-pyrimido-pyrimidines

From the 4,6,8 - trichloro - pyrimidopyrimidine and the corresponding amines at elevated temperature, if desired under pressure and with the addition of copper salts.

a) 4,6,8-tris(methylamino)-pyrimidopyrimidine

4.8 g (0.02 mol) of 4,6,8-trichloro-pyrimidopyrimidine were warmed to 200° for about 2 hours in a tube with 50 ccs (about 0.2 mol) of an absolute alcoholic-methylamine solution and 0.1 g of copper sulphate. After taking the reaction-mixture up in about 300 ccs of water the solution was filtered and evaporated to ½

of its volume. After standing for several hours the crude pyrimidopyrimidine-derivative separated as a brown, cottonwool-like deposit. Yield 4 g (91% of theory). For analysis it was recrystallized three times from water and the obtained, colourless, very fine, woolly fibres dried at 130° and 0.1 Torr, Mp. = 188—189°.

$C_9H_{13}N_7$ Mol. weight = 219.3 calc: C 49.31 H 5.97 found: 49.00 5.79

For example among others the following 4,6,8-triamino-pyrimidopyrimidines were produced analogous to the compound a):

b) 4,6,8-tris(ethylamino)-pyrimidopyrimidine, Mp. = 83—85°.

c) 4,6,8-tris(propylamino)-pyrimidopyrimidine, Mp. = 84—86°.

d) 4,6,8-tris(dimethylamino)-pyrimidopyrimidine, Mp. = 92—93°.

e) 4,6,8-tri-(β-hydroxyethylamino)-pyrimidopyrimidine, Mp. = 83—85°.

f) 4,6,8-trimorpholino-pyrimidopyrimidine, Mp. = 182—184°.

g) 4,6,8-trianilino-pyrimidopyrimidine, Mp. = 203—204°.

h) 4,6,8-tri-(p-chloro-anilino)-pyrimidopyrimidine, Mp. = 274—275°.

i) 4,6,8-tri-(o-methoxy-anilino)-pyrimidopyrimidine, Mp. = 214—215°.

Example 29.

6-alkoxy-4,8-dimorpholino-pyrimidopyrimidines

From 6-chloro-4,8-dimorpholino-pyrimidopyrimidine and the corresponding sodium alcoholate-solutions, if desired under pressure.

a) 6-ethoxy-4,8-dimorpholino-pyrimidopyrimidine.

6.7 g (0.02 mol) of 6-chloro-4,8-dimorpholino-pyrimidopyrimidine were heated to 180° for 2 hours in a bomb-tube with 50 ccs of sodium alcoholate-solution with a content of 0.5 g (0.022 mol) of sodium. The crude reaction-product was rinsed out with a little water and after the removal by suction recrystallized from ethanol-water (1:4). Yield 5.9 g (85% of theory). For analysis the compound was recrystallized twice from about 100 ccs of ethanol, once reprecipitated from hot 0.5 N-hydrochloric acid and recrystallized once more from ethanol. The thus obtained almost colourless, very short, rhomboidal prisms were dried at 65° and 0.1 Torr. Mp. = 129—132°.

$C_{14}H_{22}O_3N_6$ Mol. weight: 346.4 calc.: C 55.48 H 6.40 found: 55.11 6.20

For example the following 6-alkoxy-4,8-dimorpholino-pyrimidopyrimidines were produced analogous to compound a):

b) 6-butoxy-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 109—111°.

c) 6-(β-diethylamino-ethoxy)-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 100—103°.

d) 6-(β-ethoxy-ethoxy)-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 111—112°.

e) 6-(β-propoxy-ethoxy)-4,8-dimorpholino-pyrimidopyrimidine, Mp. = 122—123°.

Example 30.

2,6-dimorpholino-4,8-di-(β-propoxy-ethoxy)-pyrimidopyrimidine

From 2,6-dichloro-4,8-di-(β-propoxy-ethoxy)-pyrimidopyrimidine and morpholine.

8.1 g (0.02 mol) of 2,6-dichloro-4,8-di-(β-propoxy-ethoxy)-pyrimidopyrimidine (Mp. = 78—81°, produced from tetrachloro-pyrimidopyrimidine with a solution of sodium in ethylene glycol monopropyl ether with cooling) were heated to 100° for 2 hours in a bomb tube with 20 ccs of morpholine. The reaction-product was rinsed from the tube with 200 ccs of water, removed by suction, washed and dried. Yield 9.9 g (98% of theory). For analysis the compound was reprecipitated once from 1N-hydrochloric acid and recrystallized twice from methanol-water (1:4). Luminous yellow, microcrystalline powder, Mp. = 122—124°.

$C_{24}H_{42}O_6N_6$ Mol. weight: 506.6 calc.: C 56.90 H 7.56 found: 56.54 7.47

Almost all tetraamino-pyrimidopyrimidines and most triamino and diamino-pyrimidopyrimidines are cardio-vascularly active. Whereas even with very low doses an excellent coronary-dilatory effect is to be found, without materially influencing the blood-pressure, a good blood pressure reducing effect shows itself at higher dosage (from about 0.5—1mg/kg), which is conditioned by a general vasodilation and reduction of the peripheral resistance. Apart from the coronaries particularly also the cerebral vessels are dilated, which is manifested by a distinct and relatively long-lasting increase of blood circulation.

That the mentioned effects are not combined with damage to the heart, was proved with 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimidopyrimidine. On the ordinary this substance brings about a clear improvement of the cardiac efficiency. The therapeutic scope of the compounds hitherto examined is significantly great.

As examples of substances outstandingly

effective in the above-stated manner the following may be mentioned: 2,6-bis(diethanolamino) - 4,8-dipyrrolidino - pyrimido[5,4-d]-pyrimidine, 2,6-bis(diethanolamino)-4,8-bis-(diethylamino) - pyrimido[5,4-d]pyrimidine, 2,6 - bis - (diethanolamino)-4,8-dimorpholino-pyrimido[5,4-d]pyrimidine, 2,6-dimorpholino-4,8 - di - (propyl - ethanolamino) - pyrimido [5,4-d]pyrimidine, 2,6 - dimorpholino-4,8-bis (diethanolamino) - pyrimido[5,4-d]pyrimidine, 2,6 - bis(diisopropanolamino) - 4,8 - dipiperidino - pyrimido[5,4-d] pyrimidine, 2,6-di-(methyl - ethanolamino) - 4,8 - dipiperidino-pyrimido [5,4-d]pyrimidine, 2,6-dimorpholino - 4,8-di-(methyl-ethanolamino) pyrimido [5,4-d]pyrimidine, 2,4,6,8 - tetra - (methyl-ethanolamino) - pyrimido [5,4-d]pyrimidine, 4,6,8-trimorpholino-pyrimido [5,4-d] pyrimidine, 6 - diethanolamino - 4,8-dimorpholino-pyrimido [5,4-d] pyrimidine, 4,6,8-tri-methylamino-pyrimido [5,4-d] pyrimidine, 6-morpholino - 4,8-bis(ethylamino)-pyrimido[5,4-d] pyrimidine, 6-morpholino-4,8-diamino-pyrimido [5,4-d]pyrimidine, 4,8 - bis(methylamino)-pyrimido [5,4-d]pyrimidine, 4,8-bis (dimethylamino)-pyrimido [5,4-d]pyrimidine.

With respect to effective-strength and duration the said compounds are all substantially more effective than theophylline and the best thereof are considerably more effective than papaverine.

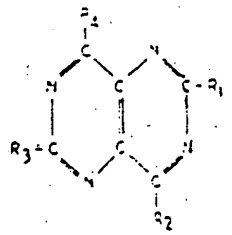
Besides the cardiovascular effect in most of the substances a good spasmolytical effect was established, which closely approximates that of papaverine; e.g. in 2,6-di(ethyl-ethanolamino) - 4,8-dimorpholino-pyrimido [5,4-d]-pyrimidine, 2,6-dimorpholino-4,8-di-(propyl-ethanolamino)-pyrimido [5,4-d]pyrimidine, 6-morpholino - 4,8 - di - (ethyl-ethanolamino)-pyrimido [5,4-d]pyrimidine, 6-morpholino-4,8-bis-(ethylamino)-pyrimido [5,4-d]pyrimidine.

In addition to the cardiovascular effect 4,6,8 - tri - methylamino-pyrimidopyrimidine also shows diuretic effect, which corresponds to that of theophylline, but lasts materially longer.

6 - (β-diethylamino-ethoxy)-4,8-di-morpholino-pyrimidopyrimidine furthermore shows a considerably better coronary-dilatory effect than theophylline with only moderate blood pressure reduction. 2,6-dimorpholino-4,8-bis (propyl - ethanolamino) - pyrimidopyrimidine has apart from a cardiovascular also a diuretic effect.

WHAT WE CLAIM IS:—

1. Process for the production of derivatives of pyrimido [5,4-d]pyrimidine, which comprises reacting pyrimido [5,4-d]pyrimidine-derivatives of the general formula:—



II

wherein at least one of the symbols R_1—R_4 which may be the same or different represents a halogen-atom, whilst the remaining residues signify hydrogen, a substituted hyroxyl group, or an amino or thio group or the residue of a heterocyclic ring, with compounds of the general formula:—

H—R or Me—R III

wherein R represents bromine, iodine, a substituted hydroxyl group or a free or substituted amino, thio, guanidino or hydrazino group or the residue of a heterocyclic ring and Me represents an alkali-metal atom.

2. A process as claimed in claim 1 in which the reaction is carried out in an inert solvent or diluent.

3. A process as claimed in any of the preceding claims, in which the reaction is carried out in the presence of an acid-binding agent and/or reaction accelerator.

4. A process as claimed in any of the preceding claims in which the reaction is carried out at temperature within the range of from —20 to 250 C.

5. A process as claimed in any of the preceding claims in which where more than one halogen-atom is available for exchange, the reaction is carried out stepwise.

6. A process as claimed in any of the preceding claims in which the reaction is carried out in the presence of water, alcohol, acetone, dioxan, benzine, xylene or dimethylformamide.

7. A process as claimed in any of the preceding claims in which the reaction is carried out under pressure.

8. A process as claimed in any of the preceding claims in which the second reaction-component is used in excess.

9. A process as claimed in any of claims 3—8 in which the acid binding agent is an alkali metal hydroxide, alkali metal carbonate or a tertiary amine.

10. A process as claimed in any of preceding claims 3—9 in which copper-powder, a copper salt is used as reaction accelerator.

11. 2,6 - bis(diethanolamino, - 4,8-dipiperidino-pyrimido [5,4-d]pyrimidine.

12. 2,6 - bis(diethanolamino)-4,8-dipyrrolidino-pyrimido [5,4-d]pyrimidine.

13. 2,6-bis (diethanolamino)-4,8-bis(diethylamino)-pyrimido [5,4-d]pyrimidine.

14. 2,6-bis(diethanolamino)-4,8-dimorpholino-pyrimido [5,4-d]pyrimidine.

15. 2,6-dimorpholino-4,8-di(propyl-ethanolamino)-pyrimido [5,4-d]pyrimidine.

16. 2,4,8-trimethylamino-homopurine.

17. As new compounds pyrimido [5,4-d] pyrimidines substituted in at least one of the 2-, 4-, 6- and/or 8-positions by one or more of the following atoms or groups: halogen, amino, mono substituted amino, disubstituted amino, ether, thio, thioether, hydrazino, guanidino, or heterocyclic groups, which groups may in turn be substituted.

18. The new compounds claimed in claim 17 in which at least two of 2-, 4-, 6- and/or 8-positions are substituted by one or more of the stated atoms or groups.

19. As new compounds pyrimido [5,4-d] pyrimidines substituted in at least two of the 2-, 4-, 6- and/or 8-positions by one or more of the following atoms or groups; chloro-, bromo, iodo, amino, aliphatic mono- or disubstituted amino groups which may bear hydroxy substituents, aromatic mono- or disubstituted amino groups, morpholino, alkoxy, carboxyalkylmercapto, hydrazino, aryloxy, guanidino, alkylmercapto and arylmercapto groups each of which groups may be substituted.

20. The new compounds claimed in any of claims 17—19 in which at least three of the 2-, 4-, 6- and/or 8-portions are substituted by one or more of the stated atoms or groups.

21. The new compounds claimed in any of claims 17—19 in which all of the 2-, 4-, 6- and 8-positions are substituted by one or more of the stated atoms or groups.

22. As new compounds 2,6-bis(diethanolamino) - 4,8 - bis(dimethylamino) - pyrimido [5,4-d]pyrimidine, 2,6-di-morpholino-4,8-bis (diethanolamino)-pyrimido [5,4-d]pyrimidine, 2,6 - bis(diisopropanolamino) - 4,8 - dipiperidino - pyrimido [5,4-d]pyrimidine, 2,6 - di-(methyl - ethanolamino)-4,8-dipiperidino-pyrimido [5,4-d]pyrimidine, 2,6-dimorpholino-4,8 - di - (methyl - ethanol-amino)-pyrimido [5,4-d]pyrimidine, 2,4,6,8 - tetra - (methyl-ethanol - amino)-pyrimido [5,4-d]pyrimidine, 4,6,8-trimorpholino-pyrimido [5,4-d]pyrimidine, 6-diethanolamino - 4,8 - dimorpholino-pyrimido [5,4-d]pyrimidine, 4,6,8-tri-methylamino-pyrimido [5,4-d]pyrimidine, 6-morpholino-4,8-bis(ethylamino)-pyrimido [5,4-d]pyrimidine, 6-morpholino-4,8-diamino-pyrimido [5,4-d]pyrimidine, 4,8-bis(methylamino)-pyrimido [5,4-d]pyrimidine, 4,8 - bis(dimethylamino)-pyrimido [5,4-d]pyrimidine, 2,6-di-(ethyl-ethanolamino) - 4,8-dimorpholino-pyrimido [5,4-d]pyrimidine, 2,6-dimorpholino-4,8 - di - (propyl - ethanolamino) - pyrimido [5,4-d]pyrimidine, 6 - morpholino - 4,8 - di-(ethyl-ethanolamino)-pyrimido [5,4-d] pyrimidine, 6-morpholino-4,8-bis-(ethylamino)-pyrimido [5,4-d] pyrimidine, 6-(β-diethylamino-ethoxy) 4,8-dimorpholinopyrimidopyrimidine.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.